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CLINICAL COURSE OF HEMOLITIC UREMIC SYNDROME IN CHILDREN - A RETROSPECTIVE STUDY

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SUMMARY

Key words: hemolitic uremic syndrome, thrombocytopenia, acute kidney injury, children, Shiga toxin, Escherichia coli.
Hemolytic-uremic syndrome (HUS) is one of the most common etiologies for acute kidney injury (AKI) and an important cause of acquired chronic kidney disease (CKD) in children. It mainly affects infants and small children, though older children and adults may also suffer. A retrospective study was conducted between 2008-2019 in Mother and Child Institute in Chisinau. The aim of this study was to determine the demographic and clinical characteristics of HUS in children.

РЕЗЮМЕ

КЛИНИЧЕСКОЕ ТЕЧЕНИЕ ГЕМОЛИТИЧЕСКОГО УРЕМИЧЕСКОГО СИНДРОМА У ДЕТЕЙ - РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

Ключевые слова: гемолитико-уремический синдром, тромбоцитопения, острая почечная недостаточность, дети, диарея, шига токсин, кишечная палочка.
Гемолитико-уремический синдром (ГУС) является одной из ведущих причин развития острой почечной недостаточности (ОПН) у детей. ГУС считается заболеванием преимущественно детей грудного и младшего возраста, однако заболеть им могут и дети старшего возраста, и взрослые. Ретроспективное исследование было проведено в период между 2008-2019 гг. в Институте матери и ребенка в Кишиневе. Целью данного исследования было определение демографических и клинических характеристик ГУС у детей.

REZUMAT

EVOLUȚIA CLINICĂ A SINDROMULUI HEMOLITIC UREMIC LA COPII – STUDIU RETROSPECTIV

Cuvinte-cheie: sindrom hemolitic uremic, trombocitopenie, leziune renală acută, copii, diaree, Shiga toxina, Escherichia coli.
Sindromul hemolitic uremic (SHU) este o afecțiune severă, considerată una dintre cele mai frecvente cauze ale insuficienței renale acute și o cauză importantă a bolii cronice renale (BCR) la copiii mici. SHU se poate instala la orice vârstă, dar se manifestă mai des la copii cu vârsta sub 5 ani. Această lucrare constituie un studiu retrospectiv realizat în Clinica de Nefrologie a Institutului Mamei și Copilului, în perioada 2008-2019. Scopul studiului a fost de a determina caracteristicile demografice și clinice ale SHU la copii.

Introduction.
Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy characterized with the triad of microangiopathy hemolytic anemia, thrombocytopenia and acute renal impairment [1].
Recent findings discribe that due to the different etiologies, modes of pathogenesis and clinical presentations, HUS might be associated with disorders of complement, which may be hereditary and/or autoimmune, cobalamin C deficiency, or with other co-existing conditions such as human immunodeficiency virus (HIV) infection, transplantation (bone marrow and solid organ), malignancy, autoimmune diseases, drugs. At the same time current knowledge indicates that across the world, the majority of HUS are associated with gastrointestinal infection with Shiga toxin-producing enterohaemorrhagic Escherichia coli (EHEC) strains[2,3].
HUS is a life-threatening illness which occurs primarily in children younger than 5 years of age. Is a leading cause

of acute kidney injury (AKI) and chronic kidney disease (CKD) in children[3,7].

HUS was first described by Swiss pediatric hematologist Conrad von Gasser, who reported five cases of HUS, those children died in the acute phase in 1955[2].

Several years later in 1983 Karmali et al. establish a link between an increased Stx activity in fecal filtrates and sporadic post-diarrheal HUS[4].

The annual incidence has been reported to be 0,7–8 cases / 100,000 population, with seasonal and geographical variability. The disease can be encountered at any age but more frequently occurs in children younger than 6 years[2,8]. The highest incidence HUS is reported in the late summer and autumn months but may occur both sporadically and in localized epidemics.

In children ocurence of tipical is up to 85-90% of total cases, atipical HUS is roughly one-tenth of the incidence. The frequency of secondary HUS due to the coexistence of a disease or condition is not yet documented[4,5].

In Europe, SHU is caused in about 90% by the Shiga toxin produced by Escherichia coli (STEC).The most common serotype responsible of the disease is E.coli O157:H7 followed by O26:H11/H [1,4,6,7].

Other enterohemorrhagic serotypes encountered in afected children are O111/H8/H (11%), O145: 28/H- (11%) și O103/H2/H- (6%),meanwhile O55, O27, O118 and O120 strains represent less than 1% of the total cases.

In the epidemiological structure, the mortality rate of HUS is up to 7%; and a significant percentage about 12-30% of cases are affected by long-term sequelae, such as kidney or neurological injury[1,4].

Objective.

To provide an update on the understanding clinical and therapeutic concepts regarding SHU through the prism of this study.

Methods.

We conducted a retrospective study collecting data from medical records of 11 children with HUS who have been followed at the Pediatric Nephrology unit in Mother and Child Institute in Chisinau, between 2008 and 2019. Criteria for diagnosis of HUS were the presence of the clinical triad of micro-angiopathic hemolytic anaemia, thrombocytopenia and AKI.

All relevant data were recorded. The following aspects were evaluated: demographic data (age, sex, environment of origin), history, symptoms and time of onset. Also we studied laboratory data including full blood count, biochemical data and results of other instrumental investigation. We used the Schwartz Equation to estimate GFR.

Results.

In the study group, the therapeutic indications were based on clinical, imaging, laboratory criteria which evaluated over time allowed to appreciate the systemic changes.

The 11 patients (9 girls and 2 boys) were recorded with a mean age at diagnosis of 4,58±1,1 years, with the limits between 7 months and 10 years.

The distribution of children by gender shows a prevalence of SHU syndrome among girls up to 81,81% of cases. The distribution by region of provinience reflects a high rate among urban children about 72% compared to the rural area. In 90% of cases HUS in children occurred during the spring-summer season. Clinical profile of the most of the patients was dominated in a prodromal phase by diarrhea and abdominal pain.

Bloody diarrhea was present in 81,81% of children with HUS. On admission to the hospital, oliguria was present only in 2 children (18%) as a dominant symptom, other 9 children developed oligoanuria at some point during hospitalization. In 2 children, the initial sign was excessive pallor of the skin, jaundice, and the chromatic change of the urine into brown. Clinical presentation with vomiting(single or repeated) was recorded in 54,5% of cases, dehydration and fever in 81,81% of cases.

The average time from the onset of the prodromal phase to the diagnosis was 7 days. 31±2,0 constitutes the mean value of hospital days, the minimum number of days constituted 11, and the maximum number 60.

Table 1 and 2 contains sugestive laboratory values. The mean haemoglobin value at admission was 63 ± 3,37/ dL. Serum LDH was increase- 3033±44 U/L, it can be interpreted as a marker of hemolysis. The average number of platelets at admission was 28,89±6,5. One patient, had single platelets, clinically manifested by cutaneous hemorrhagic syndrome.

Conclusive signs of severe impairment of glomerular function were translated by the development of the syndrome of nitrogen retention, the mean value of serum creatinine registering 368,56±64,2 μmol/l. At the same time 2 of the patients reached maximum serum creatinine values of 680 μmol/l and 530 μmol/l respectively. An increased marked value was also found in the biochemical evaluation of blood urea with an average value of 37,1±7 mmol/l. The mean value of eGFR reached 14,3±1,4 ml/ min/1,73 m^2.

We recorded extrarenal features in about 90,9% of the cases. The gastrointestinal manifestations were in the form of hemorrhagic colitis, pancreatitis with impaired exocrine function, toxic hepatitis, acute appendicitis.

Cardiac complications were reported in 5 patients (45,45%) they developed high blood pressure, and in one patient, echocardiographic and clinical evaluation showed tricuspid valve II insufficiency, moderate pulmonary hypertension 40 mm/Hg and cardiac insufficiency CF II NYHA. Pulmonary edema was diagnosed in 2 patients during hospitalization. Neurological involvment included convulsions (2 patients), encephalopathy (3 patients), cerebral edema (2 patients). In 54,54% of patients developed dyselectronemia manifested by hyperkalaemia, hyponatremia or hypocalcemia.

Table 1. Complete blood count in prodromal phase in children with HUS

Hb g/dl	
Mean±SD	63±3,37
Median	59
Erythrocytes (x 10 ^{6}/mm^{3})	
Mean± SD	2,23±0,11
Median	2,33
Leukocytes (x 10 ^{9}/mm^{3})	
Mean± SD	8,95±1,63
Median	8,3
Thrombocytes (x 10 ^{9}/mm^{3})	
Mean± SD	28,89±6,5
Median	29

Table 2. Serum biochemistry analysis in children with HUS

Creatinine µmol/l	
Mean± SD	368,5±64
Median	368
Ureea mmol/l	
Meaân± SD	37,1±7
Median	34
Protein total g/l	
Mean± SD	58,87±3,4
Median	58
ALT (U/L)	
Mean± SD	93±22
Median	75
AST (U/L)	
Mean± SD	85,1±18
Median	64
LDH (U/L)	
Mean± SD	3033±44
Median	2756
Na µmol/l	
Mean± SD	130,7±2,8
Median	132
Kµmol/l	
Mean± SD	5,64±0,1
Median	5,67
Ca µmol/l	
Mean± SD	1,82±0,07
Median	1,88

Hemodialysis therapy was initiated in 54,54% of patients diagnosed with HUS. Hemodialysis was performed based on the following data - increased urea> 100 mg/l, creatinine> 5 mg/l, endogenic creatinine clearance <7-10 ml/min/1,73 m^{2}, metabolic acidosis, hyperkalaemia, hyperhydration.

The maximum number of hemodialysis sessions were 11. After 11 days of hemodialysis, the diuresis began to recover, and serum creatinine and ureea began to decline. Despite the polyuria in the initial phase of renal function recovery, due to the retention of still significant fluids, continuous intravenous infusion with furosemide was continued.

Endovenous infusions with 0,9% NaCl soil were performed as a symptomatic therapeutic strategy. Substitution therapy in severe anemia was performed with red blood cell and freshly frozen plasma.

One patient with HUS died developing Multiple Organ Dysfunction Syndrome, the oliguria settled in 4 days after the appearance of frequent diarrhea, vomiting. HUS in this case was complicated with pleural effusion, ascites, hypertension, pancreatitis.

Discussion.

Acute renal injury is characterized by progression to oligoanuria and severe electrolyte imbalances, which require renal replacement therapy in 50% -70% of patients. Acute renal injury in STEC-HUS patients ranges from asymptomatic urinary sediment abnormalities to severe renal failure and end-stage renal disease [9].

The clinical course of a majority of patients with typical HUS, usualy result in a full recovery based on clinical and laboratory assessments. Nevertheless, a significant percentage are affected by long-term sequelae[10]. Systemic presentation of HUS varies greatly between patients, depending on the organs affected by the thrombotic microangiopathy process. Complications usualy include the central nervous system and the gastrointestinal, cardiac and musculoskeletal systems[11]. Several studies reveled that children with typical HUS and central nervous system, gastrointestinal or myocardial involvement have a higher morbidity and mortality rate during the acute phase of HUS[11,12].

Acording to literature data neurological impairment is one of the most severe complications of STEC-SHU, and is responsible for most patient deaths, thus contributing to the increased morbidity of the disease. Neurological manifestations are related to hypertension, electrolytic disorders (hyponatremia) and microtombosis in the central nervous system[13].

Nathanson et al. revelead neurologic involvement is associated with a severe renal disease but does not lead systematically to death or severe disability[14].

A systematic review of scientific articles mention that the diarrhea and associated gastrointestinal complaints in the prodromal phase of Stx-HUS may mimic those of ulcerative colitis, other enteric infections, and appendicitis this moment might delay the time of the diagnostic[15]. Biological pancreatitis, as well as elevated liver enzymes, occur in 20% of STEC-HUS patients but do not commonly result in organ failure[16].

Cardiac involvement are potentially life-threatening complication. We recorded poor cardiac complications the same rate is reported in the literature. Data on it's incidence in children with HUS are limited and reported mainly as isolated case reports. Although clinical manifestations of myocardial involvement in HUS are diverse, and they include myocardial dysfunction (poor peripheral perfusion and pulmonary edema), myocarditis, cardiac tamponade, dilated cardiomyopathy and even myocardial infarction[15,16].

A study from Romania conducted throught out 32 children described in 21, 65,6% of case, cardiac complication which were diagnosed at admission and during hospitalization, when left ventricular hypertrophy, diastolic dysfunction and pericarditis were the main echocardiographic findings. However, these injuries were reversible, in their majority, and following a 6-12 months follow-up, residual left ventricular hypertrophy was present in only 3 patients[17].

Current researches describe controversial data about clinical outcome in children with HUS.The illness and death rate of patients with diarrhea-associated HUS remained high. The study of Balgragean M. et al. revealed death of three patients (9,4%) of cases, during hospitalization[17]. Similar data we obtain in our study also a 9% mortality, one child died during the acute phase of the disease. HUS in children remains an important health concern. Our study emphasizes that prompt recognition is important to prevent significantly poor outcomes.

Conclusions.

HUS is a severe condition, being one of the most common causes of acute renal failure and an important cause of CKD in infants under 5 years of age. The syndrome also affects other organ systems, characterized by hematological, cardio-circulatory, digestive, hepatic, neurological dysfunctions. Surveillance of children who have sustained SHU allows the clinical paraclinical monitoring of long-term sequelae (high blood pressure, proteinuria, etc.) to reduce the risk of developing chronic kidney disease.

References

1. Sheerin NS., Glover E. Haemolytic uremic syndrome: diagnosis and management. F1000Res. 2019 Sep 25;8. pii: F1000 Faculty Rev-1690.
2. Loirat C., Fakhouri F. et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol.* 2016;31(1):15.
3. Shui-Ai Zhao, Bo-Tao Ning, Jian-Hua Mao. Clinical characteristics of children with hemolytic uremic syndrome in Hangzhou, China. *World Journal of Pediatrics*. 2017**;** vol.13, p. 183-185.
4. Fakhouri, Fadi Zuber, Julien Frémeaux-Bacchi, Véronique Loirat, Chantal. Haemolytic uraemic syndrome. *The Lancet.* 2017 Aug 12;390(10095):681-696.
5. Loirat C., Fakhouri F. et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol.* 2016;31(1):15.
6. Mody RK., Gu W., Jones TF., et al. Postdiarrheal hemolytic uremic syndrome in United States children: clinical pectrum and predictors of in-hospital death. *J Pediatr.* 2015;166:1022-1029.
7. Takashi Igarashi, Shuichi Ito, Mayumi Sako. Guidelines for the management and investigation of hemolytic uremic syndrome. *Clinical and Experimental Nephrology*.2014;DOI 10.1007/s10157-014-0995-9.
8. Goodship TH., Cook HT .et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int.* 2017;91(3):539.
9. Bowen EE., Coward RJ. Advances in our understanding of the pathogenesis of hemolytic uremic syndromes. *Am J Physiol Renal Physiol.* 2018 Mar 1;314(3):F454-F461.
10. Braune SA., Wichmann D. et al. Clinical features of critically ill patients with Shiga toxin–induced hemolytic uremic syndrome. *Crit Care Med.* 2013;41:1702-10.
11. Harkins V.J., McAllister D.A. Reynolds B.C. Shiga-Toxin E. coli Hemolytic Uremic Syndrome: Review of Management and Long-term Outcome. *Curr Pediatr Rep.* 2020; 8: 16-25.
12. Rahman RC., Cobeñas CJ., Drut R., Amoreo OR., et al. Hemorrhagic colitis in postdiarrheal hemolytic uremic syndrome: retrospective analysis of 54 children. *Pediatr Nephrol*. 2012;27(2):229-33.
13. Delmas Y., Vendrely B., Clouzeau B., et al. Outbreak of Escherichia coli O104:H4 haemolytic uraemic syndrome in France: outcome with eculizumab. *Nephrol Dial Transplant.* 2014;29(3):565-572.
14. Nathanson S., Kwon T., Elmaleh M., et al. Acute neurological involvement in diarrhea-associated hemolytic uremic syndrome. *Clin J Am Soc Nephrol.* 2010;5:1218e28.
15. Bianchi L., Gaiani F., Vincenzi F., et al. Hemolytic uremic syndrome: differential diagnosis with the onset of inflammatory bowel diseases. *Acta Biomed.* 2018;89(9-S):153-157.
16. Joseph A., Cointe A., et al. Shiga Toxin-Associated Hemolytic Uremic Syndrome: A Narrative Review. *Toxins (Basel).* 2020;12(2):67.
17. Balgradean M., Croitoru A., Leibovitz E. An outbreak of hemolytic uremic syndrome in southern Romania during 2015-2016: Epidemiologic, clinical, laboratory, microbiologic, therapeutic and outcome characteristics. *Pediatrics and Neonatology.* 2019; 60,87e94.